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## Case report

# Two pairs of brothers with juvenile idiopathic arthritis (JIA): case reports



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## ABSTRACT

This is a case report of juvenile idiopathic arthritis in two pairs of brothers followed in the Department of Pediatric Rheumatology, Universidade Federal da Bahia. Genetic involvement in juvenile idiopathic arthritis pathogenesis is clear and the risk of recurrence among siblings supports this contribution. An important landmark of this discovery involves the acknowledgment of major histocompatibility complex polymorphism contribution to juvenile idiopathic arthritis development susceptibility. Despite many advances, the numerous available studies cannot explain several implicit mechanisms in juvenile idiopathic arthritis pathogenesis yet.

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## Dois pares de irmãos com artrite idiopática juvenil (AIJ): relato de casos

## RESUMO

Relato de casos de ocorrência de Artrite Idiopática Juvenil (AIJ) em dois pares de irmãos acompanhados no serviço de reumatologia pediátrica da Universidade Federal da Bahia. O envolvimento genético na patogênese da AIJ está claro e o risco de recorrência entre irmãos corrobora esta contribuição. Um importante marco dessa descoberta envolve a confirmação da contribuição dos polimorfismos do complexo principal de histocompatibilidade (MHC) na susceptibilidade ao desenvolvimento da AIJ. Apesar de muitos progressos, os inúmeros estudos existentes ainda não são capazes de explicar diversos mecanismos implícitos na patogênese da AIJ.

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### Palavras-chave:

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## Introduction

Juvenile idiopathic arthritis (JIA) refers to a collection of chronic arthropathies in children with an onset before the age of 16 and a yet unknown etiology, but with a multifactorial influence linked to immune, infectious and genetic factors.<sup>1</sup>

The literature shows higher disease prevalence in siblings, as well as in first-degree relatives with other rheumatic diseases, thus demonstrating the magnitude of genetic contribution to disease susceptibility.<sup>2</sup> Several genetic studies have focused the understanding of major histocompatibility complex (MHC) polymorphism contribution to JIA development susceptibility. The results of these studies demonstrate associations between JIA and genes encoding HLA and non-HLA.<sup>3</sup> However, identifying genetic factors involved in JIA pathogenesis has been difficult for several reasons, including a low prevalence of familial cases and a lack of population studies estimating their risk of recurrence. Thus, few studies have been conducted and they are often based on a low number of cases.<sup>4</sup>

The authors describe JIA occurrence in two pairs of non-twin brothers.

## Case reports

### First report

NSF, an 11 years and 8 months old boy, presented with proximal interphalangeal joints (PIP) of the fingers, knee and ankle polyarthritis associated with an intermittent fever since 8 months of age. On physical examination, he had bilateral 4th finger PIP, knee, and ankle synovial thickening and swelling with preserved range of movement. Antinuclear antibodies (ANA) and rheumatoid factor (RF) were negative. The patient failed to adhere to treatment for socioeconomic reasons and was lost to follow up, but returned to the clinic with a clinically active disease 9 years later and was then accompanied by a younger brother, JPSF, a patient aged 5 years and 10 months with intermittent fever and arthritis of metatarsophalangeal, knee, and ankle joints since 9 months of age. Claudication, wrist and knee synovial thickening, bilateral knee arthritis, and a 5th-finger boutonniere deformity were noted on physical examination. ANA and RF were negative. After ruling out infectious diseases, malignancies, and other systemic autoimmune diseases, the diagnosis of polyarticular JIA (ILAR) was made for both brothers. They are currently taking naproxen, methotrexate, and etanercept (Fig. 1).

### Second report

IJS, an 8 year old boy, presented with a history of daily fever (100.4–102.2 °F), evanescent skin rash, and additive polyarthritis involving the wrists, elbows, knees, ankles, and proximal interphalangeal joints since 11 months of age. On physical examination, hepatosplenomegaly, bilateral arthritis of the knee, ankle, distal and proximal interphalangeal joints and a nodule in the 3rd left PIP were noted. ANA and RF



**Fig. 1 – Siblings with polyarticular JIA; case report 1.**

were negative, and infections, malignancies and other systemic autoimmune diseases were ruled out, thus leading to a diagnosis of systemic JIA (ILAR). The treatment started with methotrexate, naproxen, prednisolone, folic acid, and etanercept with improvement of the fever, rash, morning stiffness and articular manifestations. Three years later than the above-mentioned diagnosis, his younger brother aged 5 years was seen with a complaint of generalized joint pain for 5 months associated with right wrist and knee swelling and high evening fever with an onset two months earlier than joint features. He had anorexia and weight loss. Hepatomegaly, right wrist and knee swelling with local heat and pain on active and passive movement were noted on physical examination. ANA and RF were negative. Following the exclusion of other diseases, the diagnosis of a systemic JIA was made and treatment with indomethacin, methotrexate, and folic acid was initiated. He showed good clinical and laboratory response to treatment. They evolved to polyarticular and pauciarticular JIA, respectively (Fig. 2).

## Discussion

Despite genetic studies not being performed in those patients described, evidence suggests that JIA is a complex disorder influenced by multiple genetic and environmental factors. JIA prevalence among individuals having siblings affected by the disease is 15- to 30-fold higher than in general population and the risk of recurrence among siblings supports the genetic contribution to the disease. In addition, studies demonstrate pairs of siblings affected by JIA have similar human leukocyte antigens (HLA) and clinical features, with a concordance rate in monozygotic twins of 25%, thus suggesting a 250-fold higher prevalence than in the general population.<sup>4</sup>

There are literature reports on the effects of genetics on pairs of affected siblings or, less frequently, on twins. Baum et al. firstly described dizygotic twins concurrently having JIA with a confirmed degree of genome identity.



**Fig. 2 – Siblings aged 8 and 5 years (from left to right) with pauciarticular and polyarticular JIA; case report 2.**

Thereafter, other studies reported JIA in pairs of twins and a number of them highlighted the disease onset within a shorter time in twins than in other pairs of affected siblings.<sup>5</sup> Studies have further shown the same disease onset and course subtype among siblings, as well as different onset patterns, but a similar subsequent course, emphasizing the influence and complexity of genetic effects on JIA; however, the implicit mechanisms could not be explained.<sup>5,6</sup>

In a review study by Prahalad et al., the genetic influence on JIA development is pointed out either within or out of HLA region.<sup>7</sup>

Säilä et al. studied patients from multiplex families of JIA and observed that the only significant difference between familial and sporadic cases was an earlier onset of the disease in familial cases, with no essential difference in the disease clinical features being seen between patients from both groups.<sup>8</sup>

Maroldo et al. investigated clinical phenotypes and demographic characteristics in 183 pairs of siblings affected by JIA to determine whether differences between clinical phenotypes in the familial disease cohort compared with patients in the sporadic disease cohort existed. The results confirmed the conclusions from other studies showing a high concordance rate for the disease onset type between pairs of siblings, except for the subgroup of patients with systemic disease.<sup>9</sup> Regarding the current study, there was a concordance for the onset type only in the first case report.

A fact that stands out in the current reports is the disease onset at early ages. Al-Mayouf et al., by aiming to compare

patients with familial JIA versus sporadic JIA regarding clinical and laboratory variables, observed results that were similar to previous results regarding age of onset: patients with familial JIA were significantly younger at the disease onset and were diagnosed earlier than patients in the sporadic group. However, the high degree of concordance regarding the onset type seen in that group of cases was not consistent with previous reports. The fact that data were collected from a hospital that is the main tertiary center in the country, which could represent a cohort of patients with more severe JIA cases, would be a reasonable explanation for the results.<sup>10</sup>

Recently, Prahalad et al. performed an analysis of the largest available database and found that siblings and first-degree cousins of subjects with JIA have a higher risk to develop the disease. The relative risks (RRs) for each class of kinship were calculated through conditional logistic regression: RR in siblings and first-degree cousins was elevated compared with controls; the same fact did not occur with second-degree cousins.<sup>11</sup>

In summary, genetic involvement in JIA pathogenesis is clear; however, the ability to list the genes involved and understand the contribution of gene products to the pathogenesis will depend on large-scale well planned studies, as well as the understanding of environmental contribution to the disease triggering and perpetuation.

## Conflicts of interest

The authors declare no conflicts of interest.

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